lines 5-35, to be administered to inhibit enzymes of purine metabolism, to treat a viral, bacterial, fungal or parasitic infection, inhibiting the growth of cancer, inhibiting enzymatic activity of RNA polymerases, inhibiting enzymatic activity of adenosine deaminase and/or guanine deaminase in a patient or vertebrate animal.

However, upon close inspection of the referenced Hosmane text, there is no disclosure or teaching of inhibiting enzymatic activity of RNA polymerases, at all.

The Action stated inhibition of enzymes of purine metabolism to treat a viral, bacterial, fungal or parasitic infection, is not disclosed or taught in the Hosmane text. At column 16, line 20, Hosmane states that the compounds may "act by binding to purine receptors," however, this would not lead a person of ordinary skill in the art to the specific inhibition of enzymes of purine metabolism to treat a viral, bacterial, fungal or parasitic infection.

The Action stated inhibiting the growth of cancer is not stated in the Hosmane text. At column 16, lines 3-7, Hosmane discloses that certain compounds of the disclosed compounds are metabolic inhibitors and can be administered with anti-tumor and/or anti-viral agents to potentiate their action. A person of ordinary skill in the art would not be led to concluding that the formula II-IV compounds inhibit the growth of cancer.

Importantly, the disclosure and teachings in Hosmane can not led to the methods of using/treating, claimed in the present application. Indeed, the present application was filed based upon new and unexpected experimental results, set forth in the Examples of the application, in using the compounds of formulas II-IV.

These new and unexpected results are recited in the present claims for

1) a method of treating a viral, bacterial, fungal or parasitic infection;

2) a method of inhibiting the growth of cancer;

3) a method of inhibiting enzymatic activity of RNA polymerases; and

4) a method of inhibiting enzymatic activity of adenosine deaminase and guanine deaminase.

Hosmane contains broad disclosures of utility, but does not contain the experimental evidence of new and unexpected results of using the formula II-IV compounds set forth in the present Examples. For instance, at column 15, lines 37-38, Hosmane broadly discloses that the compounds "can be administered for the treatment of any disease or any applicable medical or non-medical condition." This disclosure captures the breadth of the utilities known at the time of the reference.

The methods of the present application could not be foreseen, and of utmost importance and contrary to the Office Action, the presently claimed methods would not be considered an inherent property of the formula II-IV compounds by a person of ordinary skill in the art.

The applicants submit that in view of the above, the Office Action provides no evidence that the presently claimed methods are an inherent property of the formula II-IV compounds.

In addition to the above, the applicants, provide the following reasons, supported by newly cited technical references, that successfully rebut the Examiner's contention of inherency.

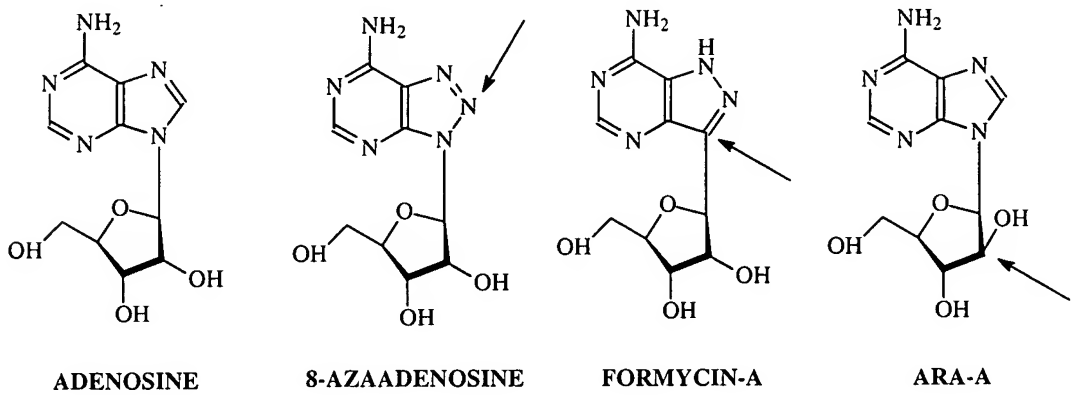
The Office Action is essentially saying that each and every compound being contemplated and synthesized everyday, targeting a particular viral or cancer enzyme or a receptor with a specific mechanism of action for each compound, by thousands of synthetic organic and medicinal chemists in pharmaceutical companies and academic research labs around the world, would turn out just exactly as planned and would show the desired biological activity, without performing the required laboratory investigations. The following evidentiary example shows that the new and unexpected results set forth in the Examples of the present application and recited in the present claims, would not be inherent based upon the disclosure in Hosmane.

Present Evidentiary Example: Inhibitors of Adenosine Deaminase:

Adenosine is one of the four building blocks of nucleic acids, the genetic material that controls life and replication. Any adverse effect on the production or usage of adenosine would have deleterious consequences on the sustenance of life. One of the ways to counter cancer is to specifically affect the production and usage of adenosine in cancer cells without causing any effect on normal cells. While this has been the major obstacle in conquering cancer, there are several cases where this is possible. Such cases involve enzymes that have subtle differences in their molecular structures and metabolic functions in cancer cells as opposed to normal cells. In such cases, an enzyme function can be specifically targeted in cancer cells without affecting the normal cells.

Many enzymes of purine metabolism, which use adenosine as a substrate, are believed to have such subtle differences in their metabolic structures and functions.

Based on this assumption, scientists synthesized several structural analogues of adenosine and screened them for anticancer activity as well as toxicity. They discovered that a number of close structural mimics of adenosine including, but not limited to, 8-azaadenosine, formycin-A, and arabinofuranosyladenosine (Ara-A) (*see* below Figure 1), possessed the

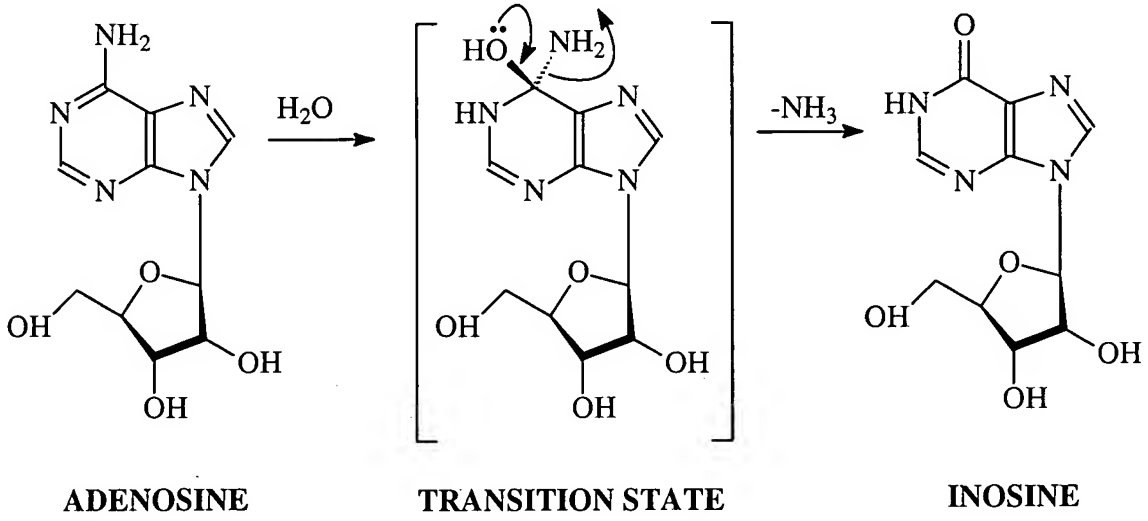


Response Figure 1: Analogues of Adenosine with Anti-Cancer Activity *In Vitro*.

desired anticancer activity and selectivity when tested in tissue culture systems (*in vitro* assays). Unfortunately, when the same compounds were tested in live animals (*in vivo*), many of the compounds were found to be either totally inactive or had greatly reduced efficacy.

Further extensive research revealed that the inactivity or reduced activity was due to the presence of an enzyme called adenosine deaminase (ADA) in high concentrations in tumor cells. The normal metabolic function of ADA is to hydrolyze adenosine into the product inosine whenever warranted by cellular demand to do so

(*see* below Figure 2). It turned out that the enzyme was capable of carrying out this conversion



ADENOSINE **TRANSITION STATE** **INOSINE**

Response Figure 2: The Established Mechanism of Hydrolysis of Adenosine to Inosine Catalyzed by ADA

not only on its natural substrate adenosine, but also on the adenosine mimics that had shown excellent anticancer activity as discussed above. The fact that the product inosine analogues had no anticancer activity explained the reason for loss of biological activity of adenosine mimics *in vivo.*

In order to restore the anti-cancer activity of adenosine mimics, the enzyme ADA needs to be inhibited. As the enzyme concentration is much higher in the cancer cells as opposed to normal cells, coupled with the likelihood of existence of subtle differences in its metabolic makeup in cancer and normal cells, the inhibition of ADA specifically in the cancer cells without significantly affecting its routine function in normal cells,

appeared possible. This raises the question of how to design an effective inhibitor against ADA. A rational inhibitor must take into account its known mechanism of action depicted in Figure 2 above. In an enzyme-catalyzed reaction, the transition state looks more like the product than the reactant, and therefore, a structure mimicking the transition state would be an effective inhibitor of the enzyme as the latter would bind more strongly to the inhibitor than its own substrate. Indeed, a natural anticancer product called coformycin as well as its 2'-deoxy analogue called pentostatin, which are the two strongest known inhibitors of ADA, are known to operate by such a mechanism.

Based on the above mechanistic rationale, coupled with the fact that the molecular structures of non-planar, non-aromatic RENS, represented by structural formulas II-IV, closely resemble those of the natural products coformycin and pentostatin, they were published as potential ADA inhibitors, and hence potential antitumor compounds. However, when a few of those analogues represented by formulas II-IV for ADA inhibition, were actually synthesized and screened, it was discovered that the subject is far more complicated than what had been originally perceived. For example, the extensive structure-activity relationship studies, as reported in the following two papers revealed that the factors governing the observed ADA inhibitory activity of a compound are not simply limited to the requirement of a transition-state-mimicking moiety within its molecular framework, instead, many other structural components of the compound also play an important role in the overall biological outcome.

1. R. S. Hosmane and M. Hong, "How Important Is the N-3 Sugar Moiety in the Tight-Binding Interaction of Coformycin with Adenosine Deaminase?" *Biochem. Biophys. Res. Commun.* **1997**, *236*, 88-93.

2. M. Hong and R. S. Hosmane, "Irreversible, Tight-Binding Inhibition of Adenosine Deaminase by Coformycins: Inhibitor Structural Features that Contribute to the Mode of Inhibition, " *Nucleosides and Nucleotides***1997**, *16*, 1053-1057.

For example, an ADA inhbitor based on REN skeleton would lose all its biological activity in spite of having incorporated a transition-state-mimicking moiety within its molecular structure if it has no ribose or an aralkyl moiety attached at the imidazole ring nitrogen. Apparently, the polar ribose hydoxyls of the sugar moiety or the non-polar phenyl group of the aralkyl moiety of the inhibitor are essential for hydrogen-bonding or hydrophobic interactions with ADA in order to render adequate stability to the enzyme-inhibitor complex.

The above example clearly illustrates that while a person of ordinary skill in the art can make reasonable general predictions based on rational mechanistic thinking, coupled with the knowledge of literature precedents on analogous compounds, the actual scientific realization of these predictions in the lab is far from being certain, and more often than not, warrants extensive further scientific research leading to major adjustments and modifications or even abandonment of original ideas. For example, some of the analogues of adenosine depicted in Figure 1, which showed potent *in vitro* anticancer activity, could not be guessed *a priori* to be totally inactive *in vivo*, nor could the reason for their inactivity be immediately reconciled with high concentrations of ADA in cancer cells without isolation, characterization, and assessment of distribution of their metabolic products. Similarly, a person skilled in the art, could not have predicted that

the removal of the ribose group from the 3-position of a REN would lead to the total loss of biological activity or the introduction of a phenyl group in place of the ribose moiety at the same position would retain considerable amount of biological activity given the fact that a ribose group is considered hydrophilic and polar, whereas a phenyl group is considered hydrophobic and non-polar.

If the Examiner desires, the above example can be provided in a Rule 132 Declaration of expert opinion.

The applicants have provided clear evidence showing that the presently claimed methods are not inherent under 35 USC 102(e) in view of the disclosure of Hosmane. The Office Action simply states that the preambles of each of the present independent claims are inherent in view of the formulae II-IV of Hosmane and nebulous description in Hosmane that contains some words similar to the preambles.

In accordance with MPEP 2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The following characteristics of the presently claimed invention have not be shown to be inherent from the Hosmane reference:

1) a method of treating a viral, bacterial, fungal or parasitic infection;

2) a method of inhibiting the growth of cancer;

3) a method of inhibiting enzymatic activity of RNA polymerases; and

4) a method of inhibiting enzymatic activity of adenosine deaminase and guanine deaminase.

The Examiner is invited to provide extrinsic evidence under MPEP 2131.01 to make clear that the missing descriptive matter is necessarily present in the claimed methods of the present application and that it would be so recognized by persons of ordinary skill.

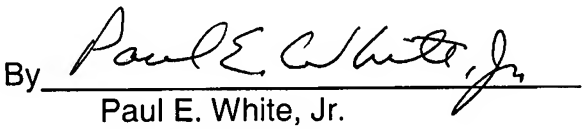
Absent such extrinsic evidence, the applicants submit that the presently claimed methods are fully allowable in view of the cited art.

Accordingly, the applicants submit that the presently claimed methods are nowhere disclosed, suggested or made obvious by the teachings of Hosmane. The presently claimed methods are not only allowable under Section 102 but are also allowable under Section 103.

In view of the above, it is believed that this application is in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

Manelli Denison & Selter, PLLC

By 

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